UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/558,350	11/23/2005	Charles Achkar	CCA-10-PCT-US	5748

7590 03/20/2008

Charles Achkar
7855 Boulevard East #221
North Bergen, NJ 07047

EXAMINER	
PACKARD, BENJAMIN J	
ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
03/20/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/558,350	ACHKAR ET AL.	
	Examiner	Art Unit	
	Benjamin Packard	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36,48 and 49* is/are pending in the application.

4a) Of the above claim(s) *6,7,9,10,13,17,19,27,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8,11,12,14-16,18,20-26,28-33,36,48 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1 pg (11/23/2005)*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group I (claims 1-36 drawn to a method of treatment) and species retinoid = 4-oxo-retinol, growth factor receptor inhibitor = Iressa, vitamin D analog = calcitriol, and chemotherapy agent = cisplatin in the reply filed on 12/17/2007 is acknowledged. The restriction and species elections are made FINAL.

Claim 6, 7, 9, 10, 13, 17, 19, 27, 34 and 35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions and species, there being no allowable generic or linking claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 8, 11, 12, 14-16, 18, 20-26, 28-33, 36, 48 and 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while possibly being enabling acute lymphoblastic leukemia and non small cell lung cancer, does not reasonably provide enablement for treating the broader disorders characterized by abnormal cell-

proliferation and/or cell-differentiation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, all Wands factors have been considered and the following factors that are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to treatment of disease, particularly treating cancer. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Suggitt and Bibby, *Clinical Cancer Research*, 2005, Vol 11, 971-981. Suggitt and Bibby teaches the unpredictability of treating cancer. Note however, that the current human tumor cell line in vitro screen is generally unpredictable. Modern methods are susceptible to false-positive and false-negative results. (page 973 1st paragraph on right-hand column). Difficulty in determining results leads to difficulty in testing for effectiveness of compounds, which leads to unpredictability in treating cancers.

2. The breadth of the claims

The claim relates to treating various forms of disorders characterized by abnormal cell-proliferation and/or cell-differentiation.

3. The amount of direction or guidance provided and the presence or absence of working examples

No reasonably specific guidance is provided concerning useful therapeutic protocols for the many types of cancer, other than the possible treatment of acute lymphoblastic leukemia and non small cell lung cancer. The latter two are corroborated by the working examples 1 and 2, where only one patient was treated in each without control groups.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably used for treatment of the many possible cancers as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 20-26, and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Gudas et al (US 5,786,391, see applicants IDS dated 11/23/2005 Cite AA).

Gudas et al discloses all-trans 4-oxo-retinol used as a biologically active agent for inducing differentiation in normal and cancer cells, for treatment of leukemias (see example VI, column 15 lines 23-60), as well as lymphomas and squamous cell carcinomas. The addition of a growth factor therapy agent is taught at column 16 lines 64-67. Growth factor therapy agents can be interpreted to include inhibitors of growth factor receptors, as shown by Adams et al (US 5,864,036) where novel substituted imidazoles are used in therapy as cytokine inhibitors by inhibiting the epidermal growth factor receptor (EGFR) (abstract and column 36 lines 24-27).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Claims 1-5, 22-26, 28, and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gudas et al (US 5,786,391, as applied to claims 1-5, 22-26, 28, and 35 above), in view of Weiner et al (Cancer Research 50, 421-425. 1990).

Gudas et al discloses all-trans 4-oxo-retinol used as a biologically active agent for inducing differentiation in normal and cancer cells, for treatment of squamous cell

carcinomas, including lung (paragraph 21). The addition of a growth factor therapy agent is taught at column 16 lines 64-67.

Does not disclose Non-small lung cancer as the squamous cell carcinomas.

Weiner et al teaches a species of the family of non-small cell lung carcinoma is the lung squamous cell carcinomas. Weiner et al does not disclose the treatments with 4–oxo-retinol.

One of ordinary skill in the art would understand that when Gudas et al teaches treating lung squamous cell carcinomas, that species is within the family which includes the treatment of non-small cell lung carcinomas.

Claims 1, 8, 11-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gudas et al (US 5,786,391, as applied to claim 1 above), in view of Njoroge et al (US Pregrant Pub 2002/0198216).

Gudas et al discloses all-trans 4-oxo-retinol used as a biologically active agent for inducing differentiation in normal and cancer cells, for treatment of leukemias (see example VI, column 15 lines 23-60), as well as lymphomas and squamous cell carcinomas.

Gudas et al does not disclose the addition of the growth factor receptor inhibitor Iressa.

Njoroge et al teaches the use of a composition containing Iressa for the treatment of proliferative disease, such as cancer (see claims 67-71), specifically disclosing non small cell lung cancer cells in the Assays on page 277 paragraph 1241.

Njoroge et al does not teach the use of 4-oxo-retinol.

One of ordinary skill in the art would have been motivated to have combined the agents of the primary and secondary references in order to provide a third chemotherapeutic composition useful for the same purpose (treating a proliferative disease, such as non small cell lung cancer). This position is consistent with well-established precedent holding that it is prima facie obvious to combine compositions known to be individually useful together so as to provide a third composition for the same use. See, e.g., In re Kerkhoven, 205 USPQ 1069, 1072 (CCPA 1980).

Claims 1, 14-16, 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gudas et al (US 5,786,391, as applied to claim 1 above), in view of Achkar (US Pregrant Pub 2001/0049365, see Applicants' IDS dated 11/23/2005 cite AB).

Gudas et al discloses all-trans 4-oxo-retinol used as a biologically active agent for inducing differentiation in normal and cancer cells, for treatment of leukemias (see example VI, column 15 lines 23-60), as well as lymphomas and squamous cell carcinomas.

Gudas et al does not disclose the addition of the vitamin D analog calcitriol.

Achkar teaches a method of treating a subject suffering from a disorder characterized by abnormal cell-proliferation and/or cell-differation, comprising administering a composition of vitamin D analog and retinoid 4-oxo-retinol (claim 9 and claim 10), where the vitamin D analog can be calcitriol (claim 3 and 4).

Ackar does not teach the addition of a growth factor therapy agent.

One of ordinary skill in the art would have been motivated to have combined the agents of the primary and secondary references in order to provide a third chemotherapeutic composition useful for the same purpose (treating disorder characterized by abnormal cell-proliferation, such as squamous cell carcinomas). This position is consistent with well-established precedent holding that it is prima facie obvious to combine compositions known to be individually useful together so as to provide a third composition for the same use. See, e.g., In re Kerkhoven, 205 USPQ 1069, 1072 (CCPA 1980).

Claims 1, 18, 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gudas et al (US 5,786,391, as applied to claim 1 above), in view of Njoroge et al (US Pregrant Pub 2002/0198216).

Gudas et al discloses all-trans 4-oxo-retinol used as a biologically active agent for inducing differentiation in normal and cancer cells, for treatment of leukemias (see example VI, column 15 lines 23-60), as well as lymphomas and squamous cell carcinomas.

Gudas et al does not disclose the addition of the chemotherapeutic agent cisplatin.

Njoroge et al teaches the use of a composition containing Iressa for the treatment of proliferative disease, such as cancer (see claims 67-71), specifically disclosing non small cell lung cancer cells in the Assays on page 277 paragraph 1241.

Njoroge et al dose not teach the use of 4-oxo-retinol.

One of ordinary skill in the art would have been motivated to have combined the agents of the primary and secondary references in order to provide a third chemotherapeutic composition useful for the same purpose (treating a proliferative disease, such as non small cell lung cancer). This position is consistent with well-established precedent holding that it is prima facie obvious to combine compositions known to be individually useful together so as to provide a third composition for the same use. See, e.g., In re Kerkhoven, 205 USPQ 1069, 1072 (CCPA 1980).

Claims 48 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gudas et al (US 5,786,391), in view of Weiner et al (Cancer Research 50, 421-425. 1990), Njoroge et al (US Pregrant Pub 2002/0198216), and Achkar (US Pregrant Pub 2001/0049365).

Gudas et al discloses all-trans 4-oxo-retinol used as a biologically active agent for inducing differentiation in normal and cancer cells, for treatment of leukemias (see example VI, column 15 lines 23-60), as well as lymphomas and squamous cell carcinomas.

Gudas et al does not disclose the addition of the chemotherapeutic agent cisplatin, the vitamin D analog calcitriol, or the addition of Iressa.

Weiner et al teaches a species of the family of non-small cell lung carcinoma is the lung squamous cell carcinomas. Weiner et al does not disclose the treatments with 4–oxo-retinol.

One of ordinary skill in the art would understand that when Gudas et al teaches treating lung squamous cell carcinomas, that species is within the family which includes the treatment of non-small cell lung carcinomas.

Njoroge et al teaches the use of a composition containing Iressa for the treatment of proliferative disease, such as cancer (see claims 67-71), specifically disclosing non small cell lung cancer cells in the Assays on page 277 paragraph 1241.

Njoroge et al dose not teach the use of 4-oxo-retinol or the vitamin D analog calcitriol.

Achkar teaches a method of treating a subject suffering from a disorder characterized by abnormal cell-proliferation and/or cell-differation, comprising administering a composition of vitamin D analog and retinoid 4-oxo-retinol (claim 9 and claim 10), where the vitamin D analog can be calcitriol (claim 3 and 4).

One of ordinary skill in the art would have been motivated to have combined the agents of the primary and secondary references in order to provide a third chemotherapeutic composition useful for the same purpose (treating a proliferative disease, such as non small cell lung cancer). This position is consistent with well-established precedent holding that it is prima facie obvious to combine compositions known to be individually useful together so as to provide a third composition for the same use. See, e.g., In re Kerkhoven, 205 USPQ 1069, 1072 (CCPA 1980).

Obviousness-Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-5,8,11,12,14-16,18,20-26,28-33,36,48 and 49 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 10-12 of U.S. Patent No. 6,242,435. Although the conflicting claims are not identical, they are not patentably distinct from each other because '435 claims the use of a retinoid and vitamin D analog for the treatment of a cell-proliferative disease. While the method does not teach the addition of growth factor receptor inhibitor Iressa or the chemotherapy agent cisplatin, as shown above in the 103 rejections, the addition of these agents would be obvious to one of ordinary skill in the art.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Benjamin Packard whose telephone number is 571-270-3440. The examiner can normally be reached on M-F 8-3:45 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Benjamin Packard/
Patent Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612